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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/635,171	08/06/2003	Dieter Heindl	21339-US	1366

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EXAMINER	
SHAW, AMANDA MARIE	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 09/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/635,171	HEINDL ET AL.	
	Examiner	Art Unit	
	Amanda M. Shaw	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 August 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-10,14,15 and 27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-10,14,15 and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 August 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the amendment filed August 11, 2006. Applicant's arguments have been fully considered but are not persuasive to overcome all grounds of rejection. All rejections not reiterated herein are hereby withdrawn. This action is made final.

Claims 1-27 are currently pending. Claims 2, 3, 11-13, and 16-26 are cancelled. Claims 1 and 27 have been amended. Therefore Claims 1, 4-10, 14-15, and 27 will be addressed herein.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

THE FOLLOWING IS A NEW GROUND OF REJECTION NECESSITATED BY APPLICANTS AMANEDMENTS TO THE CLAIMS:

Claims 1, 4-10 and 14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

In the instant case the specification does not appear to provide support for the amendment which recites "wherein said noncovalent interactions consist essentially of A/T base pair interactions" (Page 3). It is noted that the applicant points to Examples 2-8 and the entire specification for support. The specification states "the non covalent interactions may be for example nucleotide base pairing interactions and preferably A/T base pairing interactions." Additionally the specification states that "the stem generated by the base pairing interactions contains one, two, three or at least less than five additional G/C base pairs (Page 12). Further the specification teaches that, strong fluorescence signal intensities are in general obtained where at least the one, two or three terminal base pairs forming the stem are A/T base pairs" (Page 12). Thus while the specification discloses stems consisting of different ratios of A/T and G/C base pairs the specification does not provide specific support for stems which consist essentially of A/T base pair interactions.

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

THE FOLLOWING IS A NEW GROUND OF REJECTION NECESSITATED BY APPLICANTS AMANEDMENTS TO THE CLAIMS:

Claims 1, 4-10 and 14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 4-10 and 14 are indefinite over the recitation of the phrase "consist

essentially of A/T base pair interactions". This phrase in considered unclear because "consist essentially of A/T base pair interactions" is not clearly defined in the specification and there is no art recognized definition for this phrase. For example, it is unclear as to whether "consist essentially of A/T base pair interactions" refers to spacers entities that consist solely of A/T base pairs or if the spacers can also have G/C base pairs present.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 5, 10, and 27 remain rejected under 35 U.S.C. 102(b) as being anticipated by Nadeau et al (U.S. Patent 6130047) for reasons set forth in the Office Action of March 16, 2006 and reiterated below.

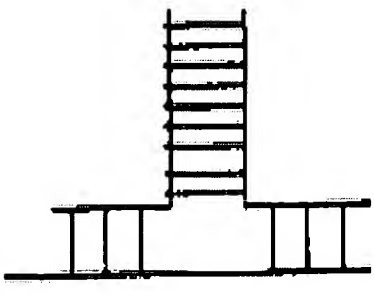
Regarding Claim 1, Nadeau et al teach a composition comprising a pair of FRET hybridization probes capable of hybridizing to a target nucleic acid sequence. Each probe comprises a nucleotide sequence entity that is complementary to a region of the target, a fluorescent entity (FRET donor or acceptor), and a spacer entity that connects the nucleotide sequence entity and the fluorescent entity; wherein the FRET hybridization probes hybridize adjacently to each other on the target nucleic acid; and

wherein the spacer entities of the FRET hybridization probes are capable of forming non covalent interactions with each other. Specifically Nadeau et al teach a detector nucleic acid comprising a 3-way oligonucleotide junction structure and two donor/acceptor dye pairs. The detector nucleic acid comprises: a target oligonucleotide (labeled at the 5' end with fluorescein), a first oligonucleotide (labeled at the 3' end with fluorescein), and a second oligonucleotide (labeled at the 5' and 3' ends with dabcyl) (Example 3 and Figure 3). The following illustrates the teachings of Nadeau: the nucleotides in red are the linkers. As you can see they hybridize to each other. The first oligo is attached to a flourescein and the second is attached to dabcyl. The blue part of the first oligonucleotide hybridizes the target sequence and the green part of the second oligonucleotide hybridizes adjacent to the first oligonucleotide on the target sequence. This would look like the figure below.

Target SEQ 5'flourescein-**GGAGCGAGCG**AA*GTGTCCTGGC*TAGAGTCTTCAAATATCAGAGCTTTACCTAACAA 3'

First Oligonucleotide 5'*GCCAGGACAC*GGAGAGG-flourescein-3'

Second Oligonucleotide 5' dabcyl-CCTCTCC**CGCTCGCTCC**-dabcyl 3'



Regarding Claim 5, Nadeau et al teach a wherein FRET acceptor entity is a Dabcyl or a Black Hole Quencher. Specifically Nadeau et al teach that the FRET acceptor is a dabcyl (Example 3).

Regarding Claim 10, Nadeau et al teach a composition wherein one of the hybridization probes is labeled at the 3' terminal end and the other of the hybridization probes is labeled at the 5' terminal end, such that upon hybridization of the probes to the target nucleic acid and excitation of the FRET donor entity, fluorescent resonance energy transfer to the FRET acceptor entity can occur Specifically Nadeau et al teach that the first oligonucleotide was labeled at the 3' end with fluorescein, and a second oligonucleotide was labeled at the 5' and 3' ends with dabcyl (Example 3).

Regarding Claim 27, Nadeau et al teach a reaction mixture for use in a dependent nucleic acid amplification reaction, comprising, in a solution: a pair of hybridization probes and at least one other component selected from the group consisting of nucleic acid amplification primers, a template dependent nucleic acid polymerase, deoxynucleoside triphosphates and a buffer suitable for use in a template dependent nucleic acid amplification reaction. Specifically Nadeau et al teach they prepared a solution containing, 50 mM TRIS-HCl, pH 8.0, 10 mM $MgCl_2$, 50 mM NaCl, 10 mM dTTP, 10 mM dCTP, 10 mM dGTP, 10 mM dATP, 5 units exo- Klenow, and varying amounts of the 3-way junction detector nucleic acid were prepared and placed in an SLM 8100 fluorometer with the sample chamber preheated to 37°C (Example 3).

RESPONSE TO ARGUMENTS REJECTED UNDER 35 U.S.C. 102(B)

5. In the response filed August 11, 2006, Applicants traversed the rejection over Nadeau by amending the claims to state that the "non covalent interactions consist essentially of A/T base pair interactions".

This argument has been fully considered but is not persuasive because in the instant case the phrase "consists essentially of" is being interpreted as open language meaning that G/C base pairs may be present in addition to A/T base pairs. Nadeau et al teach that the spacer entities that consist of 2 A/T base pairs in combination with 5 G/C base pairs. Therefore Nadeau et al does in fact teach spacer entities that consist essentially of A/T base pair interactions.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 4 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Nadeau et al (U.S. Patent 6130047) in view of Wittwer (U.S. Patent 6140054) for reasons set forth in the Office Action of March 16, 2006 and reiterated below.

The teachings of Nadeau are presented above in paragraph 4. However, Nadeau et al do not teach a set of FRET probes wherein the fluorescent entities of the

probes are selected from the group consisting of fluorescein/Cy5, fluorescein/LC Red 640, fluorescein/LC Red 705, and fluorescein/JA286.

However, Wittwer et al teach that acceptable fluorophore pairs for use as fluorescent resonance energy transfer pairs are well know to those skilled in the art and include, but are not limited to, fluorescein/rhodamine, phycoerythrin/Cy7, fluorescein/Cy5, or fluorescein/Cy5.5.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Nadeau by using one of the flourophore pairs suggested by Wittwer because they are an equally effective means for detecting nucleotides via FRET technology.

7. Claims 6 and 7 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Nadeau et al (U.S. Patent 6130047) in view of Fisher (U.S. Patent 6054568) for reasons set forth in the Office Action of March 16, 2006 and reiterated below.

The teachings of Nadeau are presented above in paragraph 4. However, Nadeau et al do not teach a composition wherein at least one of the hybridization probes includes a nucleotide having a non-natural base selected from the group consisting of a 7-deazapurine, a diamino purine and a C-nucleotide.

However Fisher et al teach during primer and probe experiments higher affinity and/or specificity to complementary nucleic acids may be achieved by the using nucleobase analogs (i.e. isoguanine and 7-deaza-isoguanine) (Column 8, lines 4-22).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Nadeau et al so as to have used a probe containing atleast one non naturally occurring base in order to have achieved the benefits set forth by Fisher which include improving the affinity and specificity of the probe hybridizing to the complementary nucleic acids.

8. Claims 8 and 9 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Nadeau et al (U.S. Patent 6130047) in view of Acton et al (U.S. Patent 6228581) for reasons set forth in the Office Action of March 16, 2006 and reiterated below.

The teachings of Nadeau are presented above in paragraph 4. However, Nadeau et al do not teach wherein at least one of the hybridization probes includes a modified sugar-phosphate backbone that contains either a 2-O methyl group or a phosphothioate.

However, Acton et al teach that nucleic acids which can be used as probes or primers can be modified to become more stable. Examples of such nucleic acids are phosphoramidate, phosphothioate and methylphosphonate analogs of DNA (Column 24, lines 65-68).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Nadeau et al so as to have used a probe containing a modified sugar phosphate backbone in order to have

achieved the benefits set forth by Fisher which include having a more stable nucleic acid.

9. Claim 14 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Nadeau et al (U.S. Patent 6130047) in view of Urdea et al (U.S. Patent 5635352) for reasons set forth in the Office Action of March 16, 2006 and reiterated below.

The teachings of Nadeau are presented above in paragraph 4. However, Nadeau et al do not teach a composition wherein said spacer entity is branched.

However, Urdea et al teach a composition wherein spacer entity is branched. Specifically Urdea et al teach amplification multimers, which are constructed so as to contain a first segment that hybridizes specifically to the nucleic acid, and a multiplicity of second segments that hybridize specifically to a labeled probe. The multimers may be either linear or branched. Branched multimers may be in the shape of a fork or a comb, with comb-type multimers preferred (Column 2, lines 1-14).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Nadeau et al so as to have used branched linkers in order to provide signal amplification in hybridization assays through networks of labeled probes. Branched mulitmers provide a convenient way to covalently attach more than one dye to an oligonucleotide.

10. Claim 15 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Nadeau et al (U.S. Patent 6130047) in view of Ahern (The Scientist) for reasons set forth in the Office Action of March 16, 2006 and reiterated below.

The teachings of Nadeau are presented above in paragraph 4. However, Nadeau et al do not teach the packaging of FRET probes along with at least one other component selected from the group consisting of nucleic acid amplification primers, a template dependent nucleic acid polymerase, deoxynucleoside triphosphates and a buffer suitable for use in a template dependent nucleic acid amplification reaction into a kit.

However, reagent kits for performing nucleotide detection assays were conventional in the field of molecular biology at the time the invention was made. In particular, Ahern discloses the general concept of kits for performing detection methods and teaches that kits provide the advantage of pre-assembling the specific reagents required to perform an assay and ensure the quality and compatibility of the reagents to be used in the assay. Ahern (page 22) also teaches that kits provide the benefits of cost-effectiveness and time efficiency. Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have packaged the FRET probes along with at least one other component selected from the group consisting of nucleic acid amplification primers, a template dependent nucleic acid polymerase, deoxynucleoside triphosphates or a buffer in a kit for the expected benefits of convenience and cost-effectiveness for practioners of the art wishing to detect nucleotide sequences using FRET probes.

RESPONSE TO ARGUMENTS REJECTED UNDER 35 U.S.C. 103(A)

11. In the response filed August 11, 2006, Applicants traversed the rejection over Nadeau by amending the claims to state that the "non covalent interactions consist essentially of A/T base pair interactions".

This argument has been fully considered but is not persuasive because in the instant case the phrase "consists essentially of" is being interpreted as open language meaning that G/C base pairs may be present in addition to A/T base pairs. Nadeau et al teach that the spacer entities that consist of 2 A/T base pairs in combination with 5 G/C base pairs. Therefore Nadeau et al does in fact teach spacer entities that consist essentially of A/T base pair interactions.

Conclusion

12. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amanda M. Shaw whose telephone number is (571) 272-8668. The examiner can normally be reached on Mon-Fri 7:30 TO 4:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Amanda M. Shaw
Examiner
Art Unit 1634

RAM R. SHUKLA, PH.D.
SUPERVISORY PATENT EXAMINER